Antiarrhythmics

Introduction

Hello, Dr. Williams here for another rant about cardiac drugs. When I first encountered this content—I know this by looking at my own med school notes—it was obvious that I invested SO MUCH energy into classes 1, 2, 3, and 4, as if that was how drugs worked. Now with a second pass, knowing what I know now and seeing the practical applications of cardiac drugs (I was responsible for the cardiac floor as a hospitalist), I cannot communicate my rage at seeing this stuff again. Only now do I realize how inappropriate and useless the historical categorization of "heart drugs" is. The work that has been done to determine what medical science now knows is still meaningful. The knowledge is essential. But the fact that all these details are known doesn't mean that anyone needs to learn them all. And just because medical science once categorized antiarrhythmic medications into four classes doesn't mean that we still have to today.

Let's just take a bird's eye view, a little *tour de drugs*, if you will. Four classes, right? Let's see . . . Class 1 are sodium channel blockers. Do you know what sodium-channel blocking antiarrhythmics cause? **Arrhythmias**. That's right, the antiarrhythmics are arrhythmogenic. Oh, and none are used in practice anymore. Well, except lidocaine, which is an anesthetic and numbs pain fibers (and is a treatment for VTach or VFib where amiodarone and electricity are not available). But oh, wait. There are actually THREE distinct class 1 subclasses: 1a, 1b, and 1c . . . and class 1c also has class 3 effects. *Wait. What?* No questions! Let's keep going. Skipping class 2 for a moment, we go to class 3. Class 3 antiarrhythmics are both potassium- and sodium-channel blockers. *So are both class 1 . . . and class 3?* No questions! **Amiodarone** is a class 3 drug. You will use that one. The other class 3 antiarrhythmics . . . guess what they cause? Yep, those too; they're **arrhythmogenic**. So far, we've got one class that is actually three subclasses and one class that shares effects with the first class, classified as a different class. *Stellar.* Does it get better? Oh, yes, it does. Class 2 are β-blockers. Oops, I already covered this one in hypertension; β-blocker is not a class because there are three subclasses. Class 4? FINALLY. Nondihydropyridine calcium-channel blockers, used for rate control, and the only class that deserves no rant. Class 1a, 1b, 1c (which is also class 3), class 2 nonselective, class 2 cardioprotective, class 2 but also α_1, class 3 that's also class 1, 2, and 4 (that's amiodarone), and class 4. *SWELL.*

Now, if this message unsettles anyone reading it, and it convinces them to go into electrophysiology cardiology (4 years of medical school, 3 years of internal medicine residency, 3 years of fellowship, and 1–2 years of subfellowship) to prove me wrong . . . more power to 'em. But the absurdity of learning the shapes of action potential changes (not ECG patterns, mind you, the action potential shapes and durations, which you never measure in clinical practice) under the influence of **medications that are not used anymore** in clinical practice is mind-boggling. If a cardiologist has a patient on an antiarrhythmic, do not stop it. There are absolutely cases in which old, dirty drugs are still indicated. I never found one case in which that was true, but then again, I didn't do a fellowship in cardiology, either. When I saw one, I asked the cardiologist if there was a good reason. When there wasn't, we chose something better and safer.

AND SO, I am going to provide you with a framework that matches more closely with clinical practice than with the science and physiology of myocytes. But it is so much easier to discuss these medications when we just say what they do clinically—**rhythm control** (back to sinus) or **rate control** (leave the rhythm, just slow down the ventricular rate).

Rate control agents **decrease automaticity** and **slow the conduction velocity** through the AV node. Rate control agents are cardioselective β-blockers and nondihydropyridine calcium-channel blockers. Oh, wait, sorry. I mean class 2 (well class 2.2 . . . cardioprotective β-blockers) and class 4 (nondihydropyridine calcium channel blockers).

Rhythm control agents get the patient out of an arrhythmia. They are particularly useful acutely in a life-threatening arrhythmia. Three agents control a fast rhythm by breaking it, two work, and one often causes serious complications, so it is rarely used. **Amiodarone** is used to quell ectopic foci (VFib, VTach, AFib), **adenosine** is used to break reentrant arrhythmias (AVNRT, AVRT/WPW, AFlutter), and **digoxin** is usually not worth its cost, but it's there for a very specific purpose (AFib with rapid ventricular response in a patient with HFrEF and in exacerbation, and you can't use amiodarone for some reason).

MYOCYTE ANTIARRHYTHMICS	PACEMAKER ANTIARRHYTHMICS
Odd-numbered classes = I and III	Even-numbered classes = II and IV
Myocyte action potential	Pacemaker action potential
Rhythm control	Rate control
Odd-numbered classes ~~Class 1 and Class 3~~ Amiodarone	Even-numbered classes ~~Class 2~~ Cardioselective β-blockers and ~~Class 4~~ Nondihydropyridine calcium-channel blockers

Table 5.1: Myocyte Antiarrhythmics vs. Pacemaker Antiarrhythmics

Then there are medications that speed up the heart. When the heart rate is too slow, there aren't many drugs that can speed it up. Those that do either don't last very long (**atropine**) or require a continuous infusion (**epinephrine, dopamine**). Instead, you are more likely to pace the patient until they can get an implantable pacemaker (the device) or whatever is causing the bradycardia is alleviated.

Arrhythmia and Unstable

What counts as unstable? Whatever you decide. We've said a MAP less than 60 is unstable, whereas others say systolic blood pressure less than 90. The point is, shock can be whatever you want it to look like. The point is, if you think there aren't minutes to obtain intravenous access and get medications, then the patient is unstable. You'll rehearse saying things like "*a systolic blood pressure less than 90 with signs of chest pain, dyspnea, or syncope is unstable.*" Fine. Whatever you determine your level of comfort to be, if you think the person will die if the rhythm isn't corrected, use electricity. If a **patient is in shock because of an arrhythmia, YOU SHOCK IT**.

Unstable arrhythmias are treated with electricity.

Fast rhythms get **shocked**—synchronized cardioversion for rhythms that are not ventricular fibrillation, unsynchronized cardioversion (defibrillation) for ventricular fibrillation. How many joules? THE PERSON IS ABOUT TO DIE. All the joules. Turn it up to 11 (that's a *Spinal Tap* reference; the max joules is 200). Varying degrees of electricity are used in stable patients who are to be converted off a bad rhythm. This happens in endoscopy suites in an environment controlled by a cardiologist.

Slow rhythms get **paced**. Pacer pads are placed on the chest, the heart rate is set on the machine, and the joules are increased until there is electrical capture—the machine zaps, and a P-QRS-T is seen. Double check mechanical capture (you can feel a pulse that matches the waveforms), and then decide if what is causing the bradycardia can be treated or call cardiology to put in a permanent subcutaneous pacemaker.

Drugs "Used" to Treat Tachycardic Arrhythmias, Overview

Read the caption before looking at this table.

CLASS	BLOCKS	CELL TYPE	CURRENTS	EFFECT OF APPLYING THE DRUG
1a	Na^+ channels (resting, open) K^+ channels	Myocyte	I_{Na} I_K	↑ Duration of phase 0 ↑ Duration of phase 3 Prolongs refractory period; also prolongs QTc
1b	Na^+ channels (inactivated)	Myocyte	I_{Na}	↑ Threshold Prevents inactivated sodium channels going to closed/resting **Shortens action potential duration of ischemic tissue
1c	Na^+ channels (all)	Myocyte	I_{Na}	↑ Duration of phase 0 No change in the duration of AP **Use-dependence, tachycardia prolongs AP
2	β_1 receptors	Pacemaker	↓ I_F ↓ I_{Ca} ↑ I_K	↓ Slope phase 4 ↑ Threshold ↓ Duration of phase 3 Decreases conduction velocity and heart rate
3	K^+ channels	Myocyte	I_K	↓ Rate of repolarization, ↑ duration of action potential Prolongs refractory period, also prolongs QTc
4	Ca^{2+} channels	Pacemaker	I_{Ca}	↑ Threshold potential ↓ Rate of phase 0 upstroke Increases refractory period

Table 5.2: Overview of Antiarrhythmics by Class
Obligatory information. Notice that the drug classes that target pacemaker myocytes (classes 2 and 4) go after conduction velocity. Drugs that target nonpacemaker myocytes (classes 1a and 3) tend to increase the duration of the phases, prolonging the refractory period. Classes 1b and 1c are subtypes because they do target sodium channels but don't behave like Class 1a regarding the refractory period. There are four classes, and there are four phases of an action potential. That is a coincidence, and there is no link between the class number and the phase of depolarization.

Class 1 Antiarrhythmics: Target Nonpacemaker Myocytes—Rhythm Control

Because this class targets Sodium Channels, and pacemaker myocytes don't use Sodium Channels, this drug class cannot affect pacemakers, so they are not useful for rate control.

Voltage-gated sodium channels open with depolarization and rapidly inactivate. Their activation gate opens with depolarization, then the inactivation gate rapidly closes. The only way they will open their inactivation gate and close their activation gate (return to resting state) is hyperpolarization and time. The rate of recovery is fastest at the resting membrane potential because it is the most negative. The rate of recovery is slower in ischemic tissue because cells may be partly depolarized at rest. All sodium-channel blockers also slow the rate of recovery in such tissues. Because the effective refractory period of any electrical cell is dependent on the sodium channels being in the closed/resting state (inactivation gate open, activation gate closed), by impairing the rate of recovery to the closed/resting state, sodium-channel blockers reduce the likelihood of action potential discharge. Because pacemakers have no sodium channels, sodium-channel blockers serve to silence nonpacemaker ectopy only. This all sounds like really good stuff.

Prolonged action potential duration, changes in the effective refractory period. All very sciencey. Too bad they are all **so arrhythmogenic that you will never use any of these drugs as antiarrhythmics**.

Blocking sodium channels to prevent action potential propagation is the mechanism of local anesthetics, such as lidocaine, epidural block, spinal tap, etc. You will see them taught in their appropriate location in Neuroscience, in the lesson on Anesthesia.

Class 1a sodium-channel blockers bind to **closed/resting** channels, **preventing them from opening**, and also bind to **already open channels**, blocking the flow of sodium through them. This directly impacts I_{Na} and, therefore, **decreases the slope** of phase 0. Class 1a also blocks **potassium channels**, decreasing I_K, and therefore they **prolong the action potential duration**. Examples of class 1a are quinidine and procainamide. **Quinidine** causes cinchonism (tinnitus, ocular dysfunction, CNS excitation). **Procainamide** causes **drug-induced lupus**. Both prolong the QT interval, increasing the risk of torsades de pointes and other fatal arrhythmias. There is no good indication for these medications. The highest-yield fact is that procainamide causes drug-induced lupus, which comes up on licensure exams (and is why it is repeated).

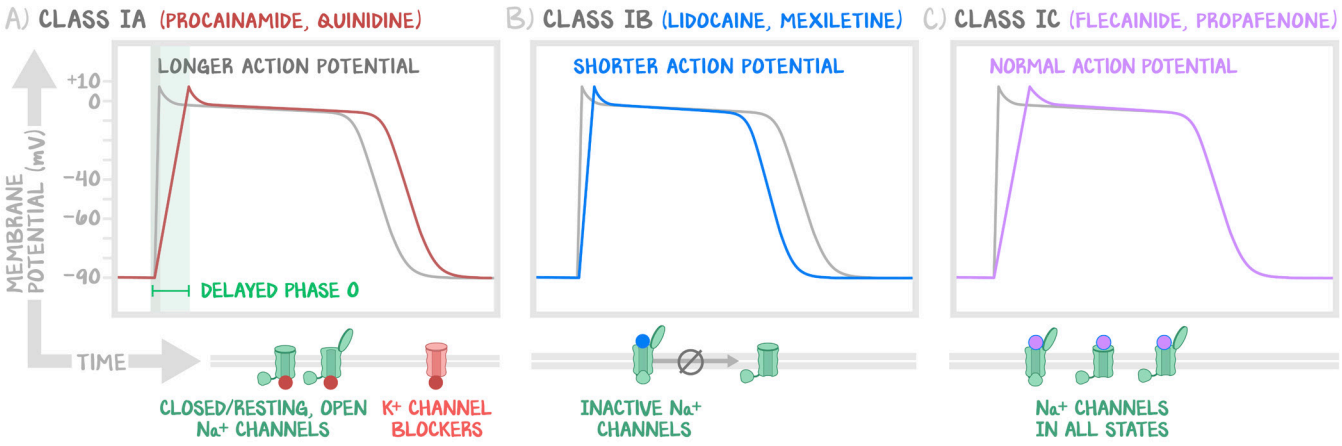

Figure 5.1: Myocyte Action Potentials on Class 1 Antiarrhythmics
(a) Class 1a, as expected, delays phase 0, extending the action potential. It also has some class 3 properties and extends phase 3. (b) Class 1b does delay phase 0, but, because of mechanisms you don't have to know, it shortens the action potential. (c) Class 1c has a pronounced phase 0 delay but no change in the action potential.

Class 1b sodium-channel blockers bind to **inactivated channels** and prevent them from returning to a closed/resting state regardless of the membrane potential and time. Because ischemic tissue already has a slower recovery rate to the closed/resting state from inactivated, Class 1b preferentially affects ischemic tissue. Because Class 1b binds to already inactivated channels, preventing them from returning to the closed/resting state, and because the opening of closed/resting channels is what drives phase 0, Class 1b has the least effect on phase 0 and actually serves to **decrease the duration** of the action potential. Medications are **lidocaine** and mexiletine. Lidocaine is used as a local anesthetic, blocking the voltage-gated sodium channels of neurons. Lidocaine can also be used in intravenous preparations to treat **ventricular tachyarrhythmias**. Its use in this way has been supplanted by amiodarone. Lidocaine can cause seizures, so caution is warranted with IV administration. By preferentially preventing ischemic tissues from returning to the closed/resting state, Class 1b silences ischemic tissue while not interfering with good tissue.

Class 1c sodium-channel blockers bind to voltage-gated sodium channels in all states with a preference for Purkinje fibers. The medications here are **flecainide** and propafenone. They exhibit a phenomenon known as use-dependence. As the heart rate increases, less time is allowed for medication to dissociate from the receptor, which increases class 1c's cumulative effects, leading to the widening of the QRS. Flecainide isn't used anymore because of its **proarrhythmic properties**.

We end this section about sodium channels with a quote from a textbook that we're not going to cite (because we use this textbook often—it is a good textbook, and we don't want to tarnish its reputation). Consider the lunacy of this statement:

"*Flecainide is the most proarrhythmic antiarrhythmic known.*" – withheld

Class 2 β-Blockers: Target Pacemaker Myocytes—Rate Control

Class 2 medications target the pacemaker myocytes, decreasing conduction velocity. Because the nonpacemaker myocytes also have β_1 receptors, nonpacemakers can also be the target of β-blocking agents (reducing the risk of fatal arrhythmias in myocardial infarction) by silencing ectopy. They are also used to reduce neurohormonal remodeling in heart failure. But you should think of class 2, the rate control agents, strictly as the **cardioselective β-blockers**. We suggested you learn only **metoprolol** (IV, PO) and **esmolol** (infusion).

At the pacemaker myocytes, adrenergic stimulation of β_1 receptors causes alterations in gene expression (longer-term changes) and changes the phosphorylation state of channels. β_1 Is stimulated by norepinephrine and epinephrine and utilizes the G_s-AC-cAMP second messenger system. The outcome is more Calcium Channels, more Funny Channels, and fewer Potassium Channels (again being vague by using more and fewer, not using words like conductance and currents).

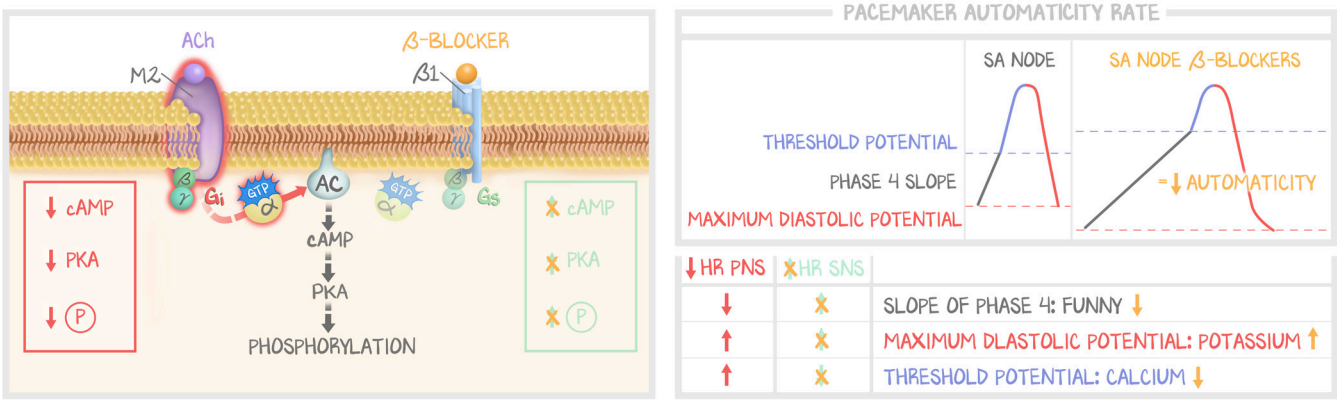

Figure 5.2: Autonomics and Class 2

Activation of β_1 leads to a lower threshold potential, steeper phase 4, and more positive maximum diastolic potential. Giving a β_1-blocker will undo that. Decreasing Calcium Channels increases the threshold potential. Increasing Potassium Channels decreases the maximum diastolic potential (makes it more negative). Decreasing Funny Channels decreases the slope of phase 4. All of this leads to a phase 4 that has farther to go (more negative maximum diastolic potential, more positive threshold potential) and goes at a slower pace (slope of phase 4).

In pacemaker myocytes, "having farther to go" and "at a slower pace" mean a **decreased heart rate**. But it also **decreases the conduction velocity** through the AV node. Pacemaker myocytes within the AV node only have Calcium Channels for their phase 0. With fewer Calcium Channels and more Potassium Channels, depolarization is impaired, and repolarization is enhanced. When used for atrial arrhythmias, such as atrial fibrillation and atrial flutter—wherein an endogenous pacemaker isn't functioning—the

main goal is to slow conduction velocity, to let fewer atrial impulses through the AV node to the ventricle. In preventing or treating ectopic depolarizations in ischemic (particularly ventricular) tissue, there is the additional benefit of reducing ectopy. In nonpacemaker myocytes, blocking β_1 also decreases Sodium Channels.

The consequence, the cost of these drugs, is that they also prevent the influx of calcium into nonpacemaker myocytes and so **decrease contractility**. When that is the goal (post myocardial infarction), that is a good thing (reducing demand). When the goal is rate control in heart failure with reduced ejection fraction, giving a β-blocker can acutely worsen ventricular function, sending the patient into cardiogenic shock. **Never start or increase a β-blocker when the patient is in an acute heart failure exacerbation.**

β-blockers, the subclasses, and their side effects have been discussed enough and will be discussed more in CAD #30: *Chronic Ischemic Heart Disease Pharmacology*.

Class 3: Potassium-Channel Blockers: Target Nonpacemaker Myocytes—Rhythm Control

Blocking potassium channels results in a weaker repolarization signal, extending the repolarization phase (phase 3, Potassium Channels). This draws out the action potential, leaving fewer opportunities for an ectopic impulse. Because there must be both repolarization and time for the Sodium Channels and Calcium Channels to return to the closed/resting state, by spending more time already depolarized, there are fewer opportunities for something to go wrong. This is visualized on the action potential graph as having a **wider action potential**, an extended action potential duration. This expands the effective refractory period, silencing nonpacemakers. It turns out that widening the action potential widens out the T-wave, increasing the chance of torsades (Q on T phenomenon).

Amiodarone is the only drug in this class you should consider using. But oh, wait, "class 3" amiodarone shows characteristics of every class—1, 2, 3, and 4. There is much to know about amiodarone. Its effect as a class 3 drug, its principal class effect, makes amiodarone a rhythm-control agent. It is used intravenously during cardiac arrests that are demonstrating either VTach or VFib. When in a controlled setting, amiodarone is used prior to and after cardioversion to normal sinus rhythm. But because it has properties of class 2 and class 4, it can also be practically used as a rate-control agent, specifically in the case of HFrEF in exacerbation with atrial fibrillation with rapid ventricular response. β-Blockers (class 2) and nondihydropyridine calcium-channel blockers (class 4) have too potent an effect on nonpacemaker myocytes such that they induce a reduced ejection fraction, worsening cardiac function, and precipitate cardiogenic shock. Amiodarone can be given as an infusion for atrial fibrillation to control the rate without the deleterious effects on the myocardium. Amiodarone has a **half-life of 80 days** and a **massive volume of distribution**, and it causes **lots of side effects**. The two you should be aware of are **thyrotoxicosis** (acutely) and **pulmonary fibrosis** (chronically). Amiodarone deposits and leads to fibrosis in all tissues, but pulmonary fibrosis is the highest yield to know about. Young patients are not placed on amiodarone because the long-term effects of fibrosis are too certain when the patient has decades to live yet. Amiodarone is preferred in older patients, as they will not live long enough to experience the consequences of fibrosis.

Sotalol, ending in -alol is both a β-blocker (class 2) and a class 3 antiarrhythmic. Sotalol causes arrhythmias, including torsades. Do not use sotalol. Learn it as the nonselective β-blocker that causes arrhythmias. Other drugs to recognize in this class are ibutilide and dofetilide. Because they prolong the QT interval and increase the chances of the Q-on-T phenomenon that leads to torsades de pointes, they are arrhythmogenic and therefore should not be used.

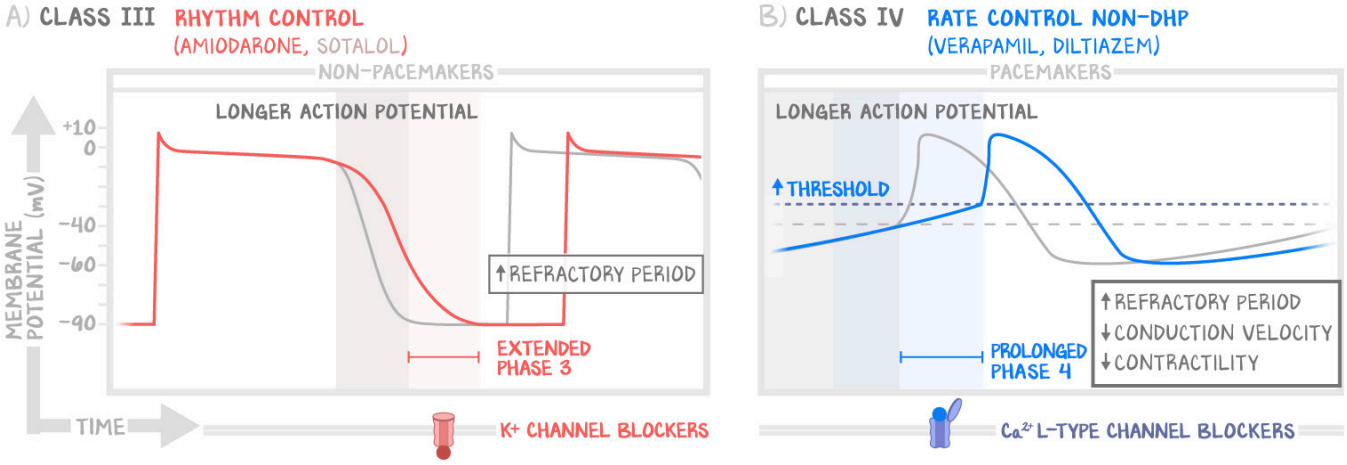

Figure 5.3: Action Potentials on Drugs
(a) Myocyte action potential changes on Class 3. (b) Pacemaker action potential changes on Class 4.

Class 4: Calcium-Channel Blockers: Target Pacemaker Myocytes—Rate Control

Class 4 drugs bind to **open calcium channels** on pacemaker myocytes. Because the action potential threshold is dependent on the number of calcium channels in the resting/ready position (inactivation gate open, activation gate closed), binding to open channels, thereby preventing their return to resting/ready, will **increase the action potential threshold**. In pacemaker myocytes, that decreases automaticity and, most importantly, **slows down the conduction velocity**.

Verapamil and **diltiazem** are used for **rate control** of AFib and AFlutter. Because they inhibit L-type calcium channels, they can also provoke a reduction in the ejection fraction, similar to β-blockers. Never use calcium-channel blockers in acute decompensated heart failure. "*They have not, however, been shown to be cardioprotective in heart disease*," says a prominent textbook. Why, thank you, Captain Textbook! Dare we say, "duh-doi?" *Cardioprotection* is derived from preventing the trophic signal by preventing the gene alterations that chronic β_1-stimulation causes.

Unclassified

Adenosine. Adenosine is used to break **reentrant rhythms**. It doesn't matter where they are—AV node, bundle of Kent, atrium, ventricle—the objective is to silence everyone and let the SA node reassume charge as the pacemaker of the heart. The reentry circuit starts when a perfectly timed beat strikes a conduction system with the ability to enter a reentry circuit (usually already diseased with unidirectional block). This perfectly timed beat is unlikely to happen. But once the circuit is established, it is self-perpetuating. If the circuit was broken, it is unlikely to happen again in the immediate time near the breaking of the circuit. All of this rationale is important, as we will see next.

Adenosine's half-life is 10 seconds. It is given through a large-bore IV followed by a 10-cc normal-saline bolus to ensure that the drug reaches the cardiac tissue before it is gone. Adenosine activates A_1 receptors on all myocytes. This short-lived, powerful activation of A_1 receptors results in a short-lived, powerful second messenger cascade. The A_1 receptor is a G-protein coupled receptor that acts through G_i. When activated, the drop in cAMP causes both impaired conduction velocity and decreased automaticity and silences ectopy. The assumption is that the problem is a reentrant circuit that is faster than the innate pacemaker (which should be the SA node). If the circuit is broken, the SA node can pick up control of the rate again. For 10 seconds, the circuit is silent. For 10 seconds, the pacemakers are

silent. The heartbeat stops (*the first time I, Dr. Williams, pushed adenosine into a living human was in the back of an ambulance as a brand new paramedic. No one told me they would flatline. Those 15 seconds felt like 15 minutes. I could see the monitor, and the patient could not. I asked, "how are you feeling," probably 75 times in those 15 seconds*). The circuit was created by a perfectly timed depolarization. There is no automaticity of the circuit. Now that it is silent, the circuit will not reactivate itself. When the adenosine wears off, automaticity is restored to the SA and AV nodes, but the circuit remains broken. The first node to reach the threshold is the SA node. Sinus rhythm is restored.

If the rhythm slows but does not break, use that opportunity to find out what rhythm it is. PRINT THE RHYTHM STRIP before, during, and after you push the adenosine. If given for AFib, AFlutter, or non-reentrant VTach, the rhythm will not break, but it will slow. That slowing will allow the clinician to better see the rhythm, identifying the chaotic background, the sawtooth pattern, or the failure to break VTach. If a patient is on a methylxanthine (theophylline, caffeine), higher doses of adenosine are required. No patient is on therapeutic methylxanthines in the United States, but because it was part of the ACLS treatment pathways, methylxanthine's relationship with adenosine is perpetuated. This means is that if one dose doesn't work, double the dose on the next go.

Digoxin. Digoxin has a narrow therapeutic index. It should not be used in renal failure or acute kidney injury. It can be used for atrial fibrillation with rapid ventricular response in the setting of acute decompensated heart failure where class 2 (β-blockers) and class 4 (calcium-channel blockers) are contraindicated. Digoxin was once a favored drug. That was before we had others. You should learn it as a dirty drug with no long-term benefits—get your patients OFF DIG (pronounced "dij"). Learn that if the patient has atrial fibrillation with rapid ventricular response and decompensated CHF, as long as their renal function is good, digoxin can be used acutely to control the heart rate. Better to use amiodarone, though.

Magnesium is used to treat torsades de pointes. Recognize the rhythm, give magnesium.

Treating Bradyarrhythmia aka Speeding the Heart Up

There are a limited number of medical therapies to treat bradyarrhythmia. The only mechanisms of action that drugs can have to increase heart rate are to inhibit M_2 and stimulate β_1. Both the inhibition of M_2 and the stimulation of β_1 increase automaticity (SA node) and conduction velocity (AV node). They do so by taking advantage of the normal physiologic antagonism of the GPCRs. **Inhibition of M_2** disinhibits adenylate cyclase by blocking the receptor activation coupled with G_i. **Stimulation of β_1** stimulates adenylyl cyclase by increasing the receptor associated with G_s.

Atropine is the parasympathetic blocker. We discussed it in General Pharmacology #9: *Cholinergics.* Atropine is an intravenous medication. The side effects of cholinergic medications used to treat something other than the heart have a fleeting side effect of tachycardia. Atropine is used to give time for more definitive therapy, such as a pacer or infusion medication.

Those that stimulate β_1 are the vasopressors you learned in shock. **Epinephrine** was introduced in shock as a pure vasoconstrictor because when it is used to treat shock, it is given after an inoconstrictor has been tried and failed. Epinephrine, at low doses, can be used to maintain the heart rate without electricity. **Dopamine** and **dobutamine** are alternative infusion medications.

There is **no chronic medical therapy** for a chronically slow heart. The drugs above are used until either the etiology of the bradycardia is corrected (toxins, for example) or an **implantable pacemaker** (without or without defibrillator) is placed.